Contains Nonbinding Recommendations

Draft Guidance on Ciprofloxacin; Dexamethasone

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the Office of Generic Drugs.

Active Ingredient: Ciprofloxacin; Dexamethasone

Dosage Form; Route: Suspension; drops; otic

Recommended Studies: Two options: In vitro or in vivo studies

I. In Vitro Studies:

To qualify for the in vitro option for ciprofloxacin; dexamethasone otic suspension (0.3%; 0.1%) pursuant to 21 CFR 320.24 (b)(6), under which "any other approach deemed adequate by FDA to measure bioavailability or establish bioequivalence" may be acceptable for determining the bioavailability or bioequivalence (BE) of a drug product, all of the following criteria must be met:

i. The test and reference listed drug (RLD) formulations are qualitatively and quantitatively the same (Q1/Q2).

ii. Acceptable comparative physicochemical characterizations of the test and RLD formulations. The characterization study should be performed on at least three exhibit batches of both the test and RLD products and should include:

- Comparative crystalline habit of dexamethasone
- Comparative appearance, pH, specific gravity, osmolality, and viscosity
- Comparative re-dispersibility (time required to re-disperse the formulation)
- Comparative soluble fraction of dexamethasone in the final drug product
- Comparative unit dose content (four drops per unit dose, for both APIs). Provide data for the amount of unit dose (four drops) with assay for both APIs from a minimum of 10 units from three batches each of the test and reference products. The unit dose content should be compared using population BE (95% upper confidence bound).
- Comparative drug particle and particle size distribution. The particle size distribution should be compared using population BE (95% upper confidence bound) based on D50 and SPAN (D90-D10)/D50 or polydispersity index. The applicant should provide no fewer than ten data sets from three different batches each of the test and reference products for the population BE analysis. Full profiles of the particle size distributions should also be submitted for all samples tested.

iii. Acceptable comparative in vitro drug release of dexamethasone from the test and RLD formulations. The abbreviated new drug application (ANDA) applicant should develop an in vitro dissolution method using U.S. Pharmacopoeia (USP) Apparatus Type IV or other appropriate apparatus.

iv. Acceptable comparative in vitro antimicrobial kill rates of the test and RLD formulations. Refer to the dexamethasone/tobramycin ophthalmic suspension guidance for details on this study.

II. In Vivo option: two studies

In vivo BE studies with clinical endpoint are requested for any generic ciprofloxacin/dexamethasone (0.3%; 0.1%) otic suspension that has a different inactive ingredient than the RLD, a difference of more than 5% in the amount of any inactive ingredient compared to that of the RLD, or unacceptable data from in vitro comparative studies.

1. Type of study: BE study with clinical endpoint
   Design: Randomized, double-blind, parallel, placebo-controlled, in vivo
   Strength: 0.3%; 0.1%
   Subjects: Males and nonpregnant females with acute otitis externa
   Additional comments: Specific recommendations are provided below

2. Type of study: BE study with clinical endpoint
   Design: Randomized, double-blind, parallel, in vivo
   Strength: 0.3%; 0.1%
   Subjects: Males and females aged 6 months and older with tympanostomy tubes with acute otitis media
   Additional comments: Specific recommendations are provided below

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Analytes to measure (in appropriate biological fluid): Not applicable (N/A)

Bioequivalence based on (90% CI): Clinical endpoint (both studies)

Waiver request of in vivo testing: N/A

Dissolution test method and sampling times: N/A

Additional comments regarding the BE study with clinical endpoint #1:

1. The Office of Generic Drugs (OGD) recommends conducting a BE study with a clinical endpoint in the treatment of acute otitis externa comparing the test product versus the RLD and vehicle control, each administered as 4 drops instilled into the affected ear twice daily (about 12 hours apart, for example, at 8 a.m. and 8 p.m.) for 7 days (1 week). Prior to administration, the suspension should be warmed by holding the bottle in the hand for 1-2 minutes and shaken well immediately before using. The subject should lie with the affected ear upward, then the drops should be instilled. This position should be maintained for 60 seconds to facilitate penetration of the drops into the ear canal. In the event of bilateral acute otitis externa, both ears should be treated; however, the ear with the more severe signs and symptoms at baseline, designated as the "study ear", will be used for the evaluations throughout the course of the study. The two co-primary endpoints are clinical cure (defined as complete resolution of signs and symptoms with no further requirement for antimicrobial therapy) and time to end of pain, both determined at the test of cure visit on study day 14-21 (i.e., 7-14 days after the end of treatment).

2. A placebo control arm is recommended to demonstrate that the test product and RLD are active and as a parameter to establish that the study is sufficiently sensitive to detect differences between products.

3. OGD has evaluated the need for a placebo arm in BE studies for this indication. Because some proportion of enrolled subjects will have spontaneous resolution of otitis externa, OGD recommends a placebo-controlled study with an early-escape clause stating that subjects who do not respond to therapy after 48 hours will receive standard therapy. We believe that a placebo-controlled trial is ethically acceptable, with the inclusion of an escape clause. In addition, by limiting the study population to adults who are able to consent to their own participation, the risk of subjecting young children to harmful side effects or to prolonged pain will be avoided.

4. Inclusion criteria (the sponsor may add additional criteria):
   a. Male or nonpregnant females aged 18 to 65 years.
   b. Clinical diagnosis of acute bacterial otitis externa with signs and symptoms of otalgia, edema, and tenderness.
   c. Culture-based diagnosis of acute bacterial otitis externa (i.e., positive baseline bacterial culture for the presence of *Pseudomonas aeruginosa* or *Staphylococcus aureus*). As the results of the baseline bacterial culture may not be known until after the subject has completed treatment, subjects who meet all the other inclusion/exclusion criteria may be enrolled in the study pending the results of the bacterial culture. A baseline bacterial culture negative for *Pseudomonas aeruginosa and Staphylococcus aureus* will exclude the subject from the Per Protocol (PP) and modified intent-to-treat (mITT) analyses.

5. Exclusion criteria (the sponsor may add additional criteria):
   a. Females who are pregnant, breast feeding, or who wish to become pregnant during the study period.
   b. Signs and symptoms of current episode of otitis externa began more than 21 days (3 weeks) prior to baseline.
   c. Current diagnosis or history of tympanic membrane perforation or damage or tympanostomy tubes.
   d. Current diagnosis or history of diabetes mellitus, psoriasis, otitis media, malignant otitis externa, mastoid cavities, stenosis, exostosis, or tumors of either ear.
   e. Current diagnosis of fungal or viral infection of either ear.
   f. Current diagnosis of dermatitis of the affected ear or surrounding area.
   g. Current presence of any other infection of the ears or other medical condition that might adversely impact the safety of the study participants or confound the study results.
   h. Known hypersensitivity to dexamethasone, ciprofloxacin, any member of the quinolone class of antimicrobial agents, or any component of the test or RLD.
   i. Use of any systemic antibacterial within four weeks prior to baseline.
   j. Use of any topical or otic medication in the affected ear within two weeks prior to baseline.

6. The protocol should include a list of the prescription and nonprescription/over-the-counter (OTC) drug products, procedures, and activities that are prohibited during the study, such as:
   a. Otic product administered to either ear, other than the assigned study product.
   b. Topical or systemic antibiotics, other than the assigned study product.
   c. Topical or systemic corticosteroids, other than the assigned study product.
   d. Systemic or topical immunosuppressive drugs or immunomodulators (e.g., azathioprine, infliximab, calcineurin inhibitors).

e. Assigned study product should not be used if the tympanic membrane is perforated or in the presence of viral infections of the external canal, including varicella and herpes simplex infections.
f. Subjects should be instructed to not use the assigned study product in the eyes, to avoid contaminating the dropper with material from the ear, fingers, or other sources, and to discontinue study product at the first appearance of a skin rash or any other sign of hypersensitivity or an allergic reaction.

7. Subjects who do not respond to therapy after 48 hours are to receive standard therapy (i.e., early escape clause).

8. The two co-primary endpoints are the proportion of subjects in the PP population with: 1) clinical cure (defined as complete resolution of signs and symptoms with no further requirement for antimicrobial therapy) of the study ear and 2) time to end of pain for the study ear, both evaluated at the test of cure visit on study day 14 to 21 (7 to 14 days after the end of treatment). If both ears of the subject are infected, the ear with the more severe signs and symptoms at baseline should be designated as the "study ear" and evaluated at each study visit (i.e., baseline visit, end of treatment visit, and test of cure visit).

9. During each study visit, score each of the following signs and symptoms using the following scale:
   a. **Signs**: edema, erythema, and otorrhea
   b. **Symptoms**: otalgia and tenderness
   c. **Scoring Scale**:

0	= none	(complete absence of any signs or symptoms)
1	= mild	(slight)
2	= moderate	(definitely present)
3	= severe	(marked, intense)

10. Time to end of pain for the affected ear should be evaluated at each post-baseline evaluation visit [(i.e., at both the end of treatment visit (study day 8-10) and the test of cure visit (study day 14-21)]. Throughout the study, subjects should record pain severity at least twice daily (prior to dosing) on a visual analog scale of 0 to 15 where 0 = no pain and 15 = severe pain. Each subject should record the time and date at which the study ear pain ended. The time to end of pain is the interval (in hours) between the first dose of study drug and the time when the study ear pain ended. If study ear pain continued to the end of the study, the value of the time to end of pain variable is set to the length of time between the time of the first dose of study drug and the last time point when a pain measurement was recorded. If the "time to end of ear pain" field is blank, then it should be considered that the pain did not end for the subject while the subject was under observation and the value of the time to end of pain variable is set to the length of time between the time of the first dose of study drug and the last time point when a pain measurement was recorded.

11. Post-therapy cultures are necessary only if the subject's clinical response is unsatisfactory. Routine post-therapy cultures frequently yield positive results due to the presence of normal flora or other colonization after treatment.

12. If the use of an ear wick or debridement of the ear is permitted during the study, the use of these procedures should be comparable among treatment groups.

13. The protocol should clearly define the PP, mITT, and safety populations.
    a. The PP population includes all randomized subjects who met all inclusion/exclusion criteria, had a positive baseline bacterial culture, used a prespecified proportion of the scheduled doses (e.g., 75% to 125%) of the assigned study product for the specified duration of the study, did not miss the scheduled doses for more than 3 consecutive days, and completed the test of cure visit on study day 14-21 with no protocol violations that would affect the treatment evaluation. The protocol should specify how compliance will be verified (e.g., by the use of subject diaries) and the protocol violations that would affect the treatment evaluation.
    b. The mITT population includes all randomized subjects who met all inclusion/exclusion criteria, including a positive baseline bacterial culture, used at least one dose of study product, and returned for at least one post-baseline evaluation visit.
    c. The safety population includes all randomized subjects who received study product.

14. Subjects with a negative culture at baseline should be discontinued from the study and excluded from the mITT and PP populations, but included in the safety population.

15. Subjects who discontinue because of lack of treatment effect after completing two days of treatment should be analyzed in the mITT and PP populations as a treatment failure. Subjects discontinued for other reasons, including drug-related adverse events, should be excluded from the PP population, but included in the mITT population using Last Observation Carried Forward (LOCF).

16. The start and stop dates of concomitant medication use during the study should be provided in the data set in addition to the reason for the medication use. The sponsor should clearly explain whether the medication was used prior to baseline visit, during the study, or both. The use of analgesics should be compared between treatment groups.

17. All adverse events (AEs) should be reported, whether or not they are considered to be related to the treatment. The report of AEs should include date of onset, description of the AE, severity, relation to study medication, action taken, outcome and date of resolution. This information is needed to determine if the incidence and severity of adverse reactions is different between the test product and RLD.

18. Generally, a drug product intended for otic use contains the same inactive ingredients and in the same concentration as the RLD. For an otic drug product that differs from the RLD in preservative, buffer, substance to adjust tonicity, or thickening agent [as permitted by the chemistry, manufacturing, and controls (CMC) regulations for ANDAs, 21 CFR 314.94(a)(9)(iv)], the regulation specifies that the applicant must identify and characterize the differences and provide information demonstrating that the differences do not affect the safety or efficacy of the proposed drug product.

19. The quantitative information of inactive ingredients of the vehicle/placebo control should be provided.

20. The method of randomization should be described in the protocol. It is recommended that an independent third party generate and hold the randomization code throughout the conduct of the study in order to minimize bias. The sponsor may generate the randomization code if not

involved in the packaging and labeling of the study medication. A sealed copy of the randomization scheme should be retained at the study site and should be available to FDA investigators at the time of site inspection to allow for verification of the treatment identity of each subject.

21. A detailed description of the blinding procedure is to be provided in the protocol. The packaging of the test, reference, and placebo products should be similar in appearance to make differences in treatment less obvious to the subjects and to maintain adequate blinding of evaluators. When possible, neither the subject nor the investigator should be able to identify the treatment. The containers should not be opened by the subject at the study center.

22. Refer to 21 CFR 320.38, 320.63 and the Guidance for Industry: Handling and Retention of BA and BE Testing Samples regarding retention of study drug samples and 21 CFR 320.36 for requirements for maintenance of records of BE testing. In addition, the investigators should follow the procedures of 21 CFR 58 and ICH E6, *Good Clinical Practice: Consolidated Guideline*, for retention of study records and data in order to conduct their studies in compliance with good laboratory practices (GLPs) and good clinical practices (GCPs). Retention samples should be randomly selected from the drug supplies received prior to dispensing to subjects. Retention samples should not be returned to the sponsor at any time.

23. It is the sponsor's responsibility to enroll sufficient subjects for the study to demonstrate BE between the products.

24. To establish BE for the first primary endpoint (proportion of subjects with clinical cure), the 90% confidence interval (CI) of the test-reference difference between products must be contained within [-0.20, +0.20] for dichotomous variables (cure versus failure), using the PP population. To establish BE for the second primary endpoint (time to end of pain in the study ear), the 90% CI of the test /reference ratio must be contained within [0.80, 1.25] for continuous variables, using the PP population.

25. As a parameter for determining adequate study sensitivity, the test product and RLD should both be statistically superior to placebo/vehicle control ($p<0.05$, two-sided) for the two co-primary endpoints using the mITT population and LOCF.

26. The following statistical analysis method is recommended for equivalence testing for a dichotomous variable (cure versus failure):

    Equivalence Analysis

    Based on the usual method used in OGD for binary outcomes, the 90% CI for the difference in success proportions between test and reference treatment must be contained within [-0.20, +0.20] in order to establish equivalence.

    The compound hypothesis to be tested is:

    H_0: $p_T - p_R < -0.20$ or $p_T - p_R > 0.20$

    versus

    H_A: $-0.20 \leq p_T - p_R \leq 0.20$

where p_T = cure rate of test treatment and p_R = cure rate of reference treatment.

Let

n_T = sample size of test treatment group

cn_T = number of cured subjects in test treatment group

n_R = sample size of reference treatment group

cn_R = number of cured subjects in reference treatment group

$$\hat{p}_T = \text{c}n_T / n_T, \quad \hat{p}_R = \text{c}n_R / n_R,$$

$$\text{and se} = (\hat{p}_T(1 - \hat{p}_T)/n_T + \hat{p}_R(1 - \hat{p}_R)/n_R)^{1/2}.$$

The 90% CI for the difference in proportions between test and reference was calculated as follows, using Yates' correction:

$$L = (\hat{p}_T - \hat{p}_R) - 1.645\ \text{se} - (1/n_T + 1/n_R)/2$$

$$U = (\hat{p}_T - \hat{p}_R) + 1.645\ \text{se} + (1/n_T + 1/n_R)/2$$

We reject H_0 if $L \geq -0.20$ and $U \leq 0.20$

Rejection of the null hypothesis H_0 supports the conclusion of equivalence of the two products.

27. The following statistical analysis method is recommended for equivalence and superiority testing for the continuous variable "time to end of pain":

    Data that measure the length of time until the end of pain relief should be analyzed using survival analysis methodology. For survival analysis, if a subject has not achieved complete relief of pain by the end of the study, the subject should be considered "censored" at the end of study.

    OGD has not previously established a method for equivalence assessment of survival outcome measures. However, the statisticians propose the Kaplan-Meier product limit method (log-rank test). The analysis would be facilitated by using the LIFETEST procedure in SAS. There are also some methods for survival data equivalence test available in the literature. For example:

    1. Wellek, Stefan. A Log-Rank Test For Equivalence Of Two Survivor Functions (1993), Biometrics 49: 877-881.
    2. John Q. Su and L. J. Wei. Nonparametric Estimation For The Difference Or Ratio Of Median Failure Times (1993): Biometrics 49: 603-607.

    For the superiority analysis of time to end of pain, survival functions for the time to end of pain would be estimated by using Kaplan-Meier product limit method for each active product versus placebo. The mean/median per each arm would be summarized and the p-values from the log-

rank test (of equality of the time to end of pain distribution) would be at the 5% level (two-sided) of significance.

For the equivalence analysis for time to end of pain, the following is proposed:

The compound hypothesis to be tested is:

H_0: $m_T / m_R \leq \theta_1$ or $m_T / m_R \geq \theta_2$

versus

H_A: $\theta_1 < m_T / m_R < \theta_2$

where, m_T = median of test treatment, m_R= median of reference treatment

The standard in OGD for equivalence analyses for continuous endpoints has been θ_1=0.80 and θ_2=1.25.

Two methods could potentially be used to perform the equivalence test. The methods are illustrated for θ_1=0.80 and θ_2=1.25.

1. Perform two one-sided m_T – 0.8/1.25 m_R tests

   H_{01}: $m_T - 0.8\, m_R \leq 0$ versus H_{A1}: $m_T - 0.8\, m_R > 0$

   H_{02}: $m_T - 1.25\, m_R \geq 0$ versus H_{A2}: $m_T - 1.25\, m_R < 0$

   Multiply all of survival data, time to end of pain, from the reference product by 0.8 or 1.25, and then test the resulting data set for equality (α=0.05, one-sided test). This test would be based on the log-rank test. Rejection of both null hypotheses H_{01} and H_{02} supports the conclusion of equivalence of the two products.

2. Estimate the 90% CI by using a bootstrap method

   The 90% CIs of the median ratio m_T / m_R (corresponding to two 1-sided tests at level α=0.05) could be calculated as follows: 1) obtain medians of test and reference treatment from the Kaplan-Meier product limit method by using the PROC LIFETEST procedure in SAS®, 2) estimate the ratio m_T / m_R, 3) perform the bootstrap re-sampling approach to obtain the 90% CI for the ratio m_T / m_R.

   The null hypothesis H_0 would be rejected if the 90% CI for m_T/m_R is contained in the [0.80, 1.25] interval. Rejection of the null hypothesis H_0 supports the conclusion of equivalence of the two products.

28. Study data should be submitted to OGD in electronic format.
    a. A list of file names, with a simple description of the content of each file, should be included.
    b. Provide a PDF document with a detailed description of the codes that are used for each variable in each of the SAS data sets (for example, Y=yes, N=no for analysis population).

c. All SAS transport files should include .xpt as the file extension and should not be compressed. A simple SAS program to open the data transport files and SAS files should be included.
d. Primary data sets should consist of two data sets: No Last Observation Carried Forward (NO-LOCF-pure data set) and Last Observation Carried Forward (LOCF-modified data set).
e. Provide a separate data set for variables such as demographics, baseline admission criteria, adverse events, reasons for discontinuation of treatment, concomitant medications, medical history, compliance, comments, pain severity scale scores (from subject diary), etc.

29. Provide a summary data set containing a separate line listing for each subject (if data exist) using the following headings, if applicable:
    a. Study identifier
    b. Subject identifier
    c. Site identifier: study center
    d. Age
    e. Age units (years)
    f. Sex
    g. Race
    h. Name of actual treatment (exposure): test product, RLD, placebo
    i. Duration of treatment (total exposure in days)
    j. Completed the study (yes/no)
    k. Reason for premature discontinuation of subject
    l. Subject required additional treatment for acute otitis externa due to unsatisfactory treatment response (yes/no)
    m. PP population inclusion (yes/no)
    n. Reason for exclusion from PP population
    o. Modified intent to treat (mITT) population inclusion (yes/no)
    p. Reason for exclusion from mITT population
    q. Safety population inclusion (yes/no)
    r. Reason for exclusion from safety population
    s. Baseline edema score
    t. Baseline otalgia score
    u. Baseline tenderness score
    v. Final designation as clinical cure (yes/no)
    w. Pain relief achieved while on study (yes/no)
    x. If pain relief achieved while on study, time to relief of pain (hours)
    y. Treatment compliance: number of missed doses per subject
    z. Concomitant medication (yes/no)
    aa. Adverse event(s) reported (yes/no)

    Please refer to Table 1 as an example. This sample table may contain additional information not applicable to your study and/or it may not contain all information applicable to your study.

Table 1: Example of a summary data set containing one line listing for each subject

STUDYID	SUBJID	SITEID	AGE	AGEU	SEX	RACE	EXTRT	EXDUR	completd	disc_rs	add_trt	pp	pp_rs	mitt	mitt_rs	safety	safe_rs	edema_b	otalg_b	tender_b	clincure	pain_rel	time_rel	complian	CM	AE
101	1	01	22	YEARS	F	1	A	7	Y		N	Y		Y		Y		2	2	3	N	Y	4	0	Y	Y
101	2	01	30	YEARS	F	1	B	7	Y		N	Y		Y		Y		1	3	2	Y	Y	6	0	N	N

Note: Capitalized headings are from Clinical Data Interchange Standards Consortium (CDISC) Study Data Tabulation Model (SDTM) Implementation Guide (IG) for Human Clinical Trials V3.1.2 Final, dated 11/12/08.

STUDYID: Study identifier
SUBJID: Subject identifier for the study
SITEID: Study site identifier
AGE: Age
AGEU: Age units (years)
SEX: Sex, M=male, F=female, U=unknown
RACE: Race, e.g., 1=white, 2=Black or African American, 3=Asian, 4=American Indian or Alaska Native, 5=Native Hawaiian or other Pacific Islanders
EXTRT: Name of actual treatment (exposure), e.g., A=test product, B= RLD, C=placebo
EXDUR: Duration of treatment (total exposure in days)
completd: Completed the study, Y=yes, N=no
disc_rs: Reason for premature discontinuation of subject
add_trt: Subject required additional treatment for acute otitis externa due to unsatisfactory treatment response (yes/no)
pp: PP population inclusion, Y=yes, N=no
pp_rs: Reason for exclusion from PP population, e.g., A=prematurely discontinued, B=lost to follow-up, C=subject moved out of the area, D=noncompliant, etc.
mitt: Modified Intent to Treat (mITT) population inclusion, Y=yes, N=no
mitt_rs: Reason for exclusion from mITT population, e.g., A=never treated, B=negative baseline culture, etc.
safety: Safety population inclusion, Y=yes, N=no
safe_rs: Reason for exclusion from Safety population, e.g., A=never treated, etc.
edema_b: Baseline edema score, e.g., 0 to 3
otalg_b: Baseline otalgia score, e.g., 0 to 3
tender_b: Baseline tenderness score, e.g., 0 to 3
clincure: Final designation as clinical cure, Y=yes (clinical cure), N=no (failure)
pain_rel: Pain relief achieved while on study, Y=yes, N=no
time_rel: If pain relief achieved while on study, time to relief of pain (hours)
complian: Treatment compliance, e.g., number of missed doses per subject
CM: Concomitant medication, Y=yes, N=no
AE: Adverse event(s) reported, Y=yes, N=no

30. Provide a data set containing a separate line listing for each visit per subject (if data exist) using the following headers, if applicable:
    a. Study identifier
    b. Subject identifier
    c. Name of Actual Treatment (exposure): test product, RLD, placebo control

d. Visit number
e. Visit date
f. Number of days since baseline visit
g. Evaluator: identity of evaluator
h. Edema score
i. Erythema score
j. Otorrhea score
k. Otalgia score
l. Tenderness score
m. Composite (total) signs and symptoms score
n. Culture result
o. Concomitant medication reported during this visit (yes/no)
p. Adverse event reported during this visit (yes/no)
q. Laboratory testing during this visit (yes/no)

Please refer to Table 2 as an example. This sample table may contain additional information not applicable to your study and/or it may not contain all information applicable to your study.

Table 2: Example of data set containing one line listing for each visit per subject

STUDYID	SUBJID	EXTRT	VISITNUM	SVSTDTC	ELTMBS	EVAL	edema	erythema	otorrhea	otalgia	tender	compss	culture	CMrpt	AErpt	LBtest
101	1	A	1	2004-07-01	0	JB	0	2	1	2	0	5	Pos	Y	N	Y

Note: Capitalized headings are from Clinical Data Interchange Standards Consortium (CDISC) Study Data Tabulation Model (SDTM) Implementation Guide (IG) for Human Clinical Trials V3.1.2 Final, dated 11/12/08.

STUDYID:	Study identifier
SUBJID:	Subject identifier for the study
EXTRT:	Name of actual treatment (exposure), e.g., A=test product, B=RLD, C= placebo control
VISITNUM:	Visit sequence number
SVSTDTC:	Visit date: (SVSTDTC=Subject Visit Start Date Time-Character)
ELTMBL:	Elapsed time since baseline (days)
EVAL:	Evaluator: identity of the evaluator, e.g., initials
edema:	Edema score, e.g., 0=none (complete absence), 1=mild (slight), 2=moderate (definitely present), 3=severe (marked, intense)
erythema:	Erythema score, e.g., 0=none (complete absence), 1=mild (slight), 2=moderate (definitely present), 3=severe (marked, intense)
otorrhea:	Otorrhea score, e.g., 0=none (complete absence), 1=mild (slight), 2=moderate (definitely present), 3=severe (marked, intense)
otalgia:	Otalgia score, e.g., 0=none (complete absence), 1=mild (slight), 2=moderate (definitely present), 3=severe (marked, intense)
tender:	Tenderness score, e.g., 0=none (complete absence), 1=mild (slight), 2=moderate (definitely present), 3=severe (marked, intense)
compss:	Composite (total) signs and symptoms score

culture:	Culture, e.g., Pos=Positive for *Pseudomonas aeruginosa* or *Staphylococcus aureus*, Neg=Negative for *Pseudomonas aeruginosa* and *Staphylococcus aureus*
CMrpt:	Concomitant medication reported during this visit, Y=yes, N=no
AErpt:	Adverse event reported during this visit, Y=yes, N=no
LBtest:	Laboratory testing performed during this visit, Y=yes, N=no

31. These recommendations are specific to this product and may not be appropriate for BE studies of any other product, including any other dosage form or strength of ciprofloxacin hydrochloride and dexamethasone.

Additional comments regarding the BE study with clinical endpoint #2:

1. OGD recommends conducting a BE study with a clinical endpoint in the treatment of acute otitis media comparing the test product versus RLD, each administered as 4 drops instilled into the affected ear twice daily (about 12 hours apart, for example, at 8 a.m. and 8 p.m.) for 7 days (1 week). Prior to administration, the suspension should be warmed by holding the bottle in the hand for 1-2 minutes and shaken well immediately before using. The subject should lie with the affected ear upward, and then the drops should be instilled. The tragus should then be pumped 5 times by pushing inward to facilitate penetration of the drops into the middle ear. This position should be maintained for 60 seconds to facilitate penetration of the drops into the ear canal. In the event of bilateral acute otitis media, both ears should be treated; however, the ear with the more severe signs and symptoms at baseline, designated as the "study ear", will be used for the evaluations throughout the course of the study. The two co-primary endpoints are clinical cure (defined as complete resolution of signs and symptoms with no further requirement for antimicrobial therapy) and time to cessation of otorrhea, both determined at the test of cure visit on study day 14-21 (i.e., 7-14 days after the end of treatment).

2. Inclusion criteria (the sponsor may add additional criteria):
   a. Male or female aged 6 months to 12 years
   b. Clinical diagnosis of acute otitis media
   c. Otorrhea for 3 weeks or less
   d. Patent tympanostomy tubes

3. Exclusion criteria (the sponsor may add additional criteria):
   a. Tympanostomy tube placement 3 days or less before baseline visit
   b. Tympanostomy tubes containing silver oxide or silver salts, or T-type tubes
   c. History of diabetes mellitus or immunosuppressive disorder
   d. Current presence of any other infection of the ears or other medical condition that might adversely impact the safety of the study participants or confound the study results
   e. Known hypersensitivity to dexamethasone, ciprofloxacin, any member of the quinolone class of antimicrobial agents, or any component of the test or RLD
   f. Use of any topical or systemic antibacterial within 14 days prior to baseline visit
   g. Use of any otic medication within 7 days prior to baseline visit

4. The protocol should include a list of the prescription and over-the-counter (OTC) drug products, procedures, and activities that are prohibited during the study, such as:
   a. Otic product administered to either ear, other than the assigned study product
   b. Topical or systemic antibiotics, other than the assigned study product
   c. Topical or systemic corticosteroids, other than the assigned study product

d. Systemic or topical immunosuppressive drugs or immunomodulators (e.g., azathioprine, infliximab, calcineurin inhibitors).
e. Subjects should be instructed to not use the assigned study product in the eyes; avoid contaminating the dropper with material from the ear, fingers, or other sources; protect treatment from light; and discontinue study product at the first appearance of a skin rash or any other sign of hypersensitivity or an allergic reaction.

5. The two co-primary endpoints are the proportion of subjects in the PP population with: 1) clinical cure (defined as complete resolution of signs and symptoms with no further requirement for antimicrobial therapy) of the study ear, and 2) time to cessation of otorrhea for the study ear, both evaluated at the test of cure visit on study day 14 to 21 (7 to 14 days after the end of treatment). If both ears of the subject are infected, the ear with the more severe signs and symptoms at baseline should be designated as the "study ear" and evaluated at each study visit (i.e., baseline visit, end of treatment visit, and test of cure visit).

6. Time to cessation of otorrhea for the affected ear should be evaluated at each post-baseline evaluation visit [(i.e., at both the end of treatment visit (study day 8-10) and the test of cure visit (study day 14-21)]. Throughout the study, subjects should note the presence or absence of otorrhea at least daily in a diary. Each subject should record the time and date at which the study ear otorrhea ended. The time to cessation of otorrhea is the interval (in days) between the first dose of study drug and the time when the study ear otorrhea ended. If study ear otorrhea continued to the end of the study, the value of the time to cessation of otorrhea variable is set to the length of time between the time of the first dose of study drug and the last time point when the presence of otorrhea was recorded. If the "time to cessation of otorrhea" field is blank, then it should be considered that the otorrhea did not end for the subject while the subject was under observation and the value of the time to cessation of otorrhea variable is set to the length of time between the time of the first dose of study drug and the last time point when the presence or absence of otorrhea was recorded in the daily diary.

7. The protocol should clearly define the PP and safety populations.
   a. The PP population includes all randomized subjects who met all inclusion/exclusion criteria, had a positive baseline bacterial culture, used a prespecified proportion of the scheduled doses (e.g., 75% to 125%) of the assigned study product for the specified duration of the study, did not miss the scheduled doses for more than 3 consecutive days, and completed the test of cure visit on study day 14-21 with no protocol violations that would affect the treatment evaluation. The protocol should specify how compliance will be verified, e.g., by the use of subject diaries, and the protocol violations that would affect the treatment evaluation.
   b. The safety population includes all randomized subjects who received study product.

8. Subjects who discontinue because of lack of treatment effect after completing five days of treatment should be analyzed in the PP populations as a treatment failure. Subjects discontinued for other reasons, including drug-related adverse events, should be excluded from the PP population.

9. The start and stop dates of concomitant medication use during the study should be provided in the data set in addition to the reason for the medication use. The sponsor should clearly explain whether the medication was used prior to baseline visit, during the study, or both. The use of analgesics should be compared between treatment groups.

10. All adverse events (AEs) should be reported, whether or not they are considered to be related to the treatment. The report of AEs should include date of onset, description of the AE, severity, relation to study medication, action taken, outcome and date of resolution. This information is needed to determine if the incidence and severity of adverse reactions is different between the test product and RLD.

11. Generally, a drug product intended for otic use contains the same inactive ingredients and in the same concentration as the RLD. For an otic drug product that differs from the RLD in preservative, buffer, substance to adjust tonicity, or thickening agent [as permitted by the chemistry, manufacturing and controls (CMC) regulations for ANDAs, 21 CFR 314.94(a)(9)(iv)], the regulation specifies that the applicant must identify and characterize the differences and provide information demonstrating that the differences do not affect the safety or efficacy of the proposed drug product.

12. The method of randomization should be described in the protocol. It is recommended that an independent third party generate and hold the randomization code throughout the conduct of the study in order to minimize bias. The sponsor may generate the randomization code if not involved in the packaging and labeling of the study medication. A sealed copy of the randomization scheme should be retained at the study site and should be available to FDA investigators at the time of site inspection to allow for verification of the treatment identity of each subject.

13. A detailed description of the blinding procedure is to be provided in the protocol. The packaging of the test and reference products should be similar in appearance to make differences in treatment less obvious to the subjects and to maintain adequate blinding of evaluators. When possible, neither the subject nor the investigator should be able to identify the treatment. The containers should not be opened by the subject at the study center.

14. Refer to 21 CFR 320.38, 320.63 and the guidance for industry *Handling and Retention of BA and BE Testing Samples* regarding retention of study drug samples and 21 CFR 320.36 for requirements for maintenance of records of BE testing. In addition, the investigators should follow the procedures of 21 CFR 58 and ICH E6, *Good Clinical Practice: Consolidated Guideline*, for retention of study records and data in order to conduct their studies in compliance with good laboratory practices (GLPs) and good clinical practices (GCPs). Retention samples should be randomly selected from the drug supplies received prior to dispensing to subjects. Retention samples should not be returned to the sponsor at any time.

15. It is the sponsor's responsibility to enroll sufficient subjects for the study to demonstrate BE between the products.

16. To establish BE for the first primary endpoint (proportion of subjects with clinical cure), the 90% CI of the test – reference difference between products must be contained within [-0.20, +0.20] for dichotomous variables (cure versus failure), using the PP population. To establish BE for the second primary endpoint (time to cessation of otorrhea in the study ear), the 90% CI of the test /reference ratio must be contained within [0.80, 1.25] for continuous variables, using the PP population.

17. The following statistical analysis method is recommended for equivalence testing for a dichotomous variable (cure versus failure):

    <u>Equivalence Analysis</u>

Based on the usual method used in OGD for binary outcomes, the 90% CI for the difference in success proportions between test and reference treatments must be contained within [-0.20, +0.20] in order to establish equivalence.

The compound hypothesis to be tested is:

H_0: $p_T - p_R < -0.20$ or $p_T - p_R > 0.20$

versus

H_A: $-0.20 \leq p_T - p_R \leq 0.20$

where p_T = cure rate of test treatment and p_R = cure rate of reference treatment.

Let

n_T = sample size of test treatment group

cn_T = number of cured subjects in test treatment group

n_R = sample size of reference treatment group

cn_R = number of cured subjects in reference treatment group

$\hat{p}_T = cn_T / n_T$, $\hat{p}_R = cn_R / n_R$,

and se = $(\hat{p}_T(1 - \hat{p}_T)/n_T + \hat{p}_R(1 - \hat{p}_R)/n_R)^{½}$.

The 90% CI for the difference in proportions between test and reference was calculated as follows, using Yates' correction:

$$L = (\hat{p}_T - \hat{p}_R) - 1.645\ se - (1/n_T + 1/n_R)/2$$

$$U = (\hat{p}_T - \hat{p}_R) + 1.645\ se + (1/n_T + 1/n_R)/2$$

We reject H_0 if $L \geq -0.20$ and $U \leq 0.20$

Rejection of the null hypothesis H_0 supports the conclusion of equivalence of the two products.

18. The following statistical analysis method is recommended for equivalence and superiority testing for the continuous variable "time to cessation of otorrhea":

Data that measure the length of time until the cessation of otorrhea should be analyzed using survival analysis methodology. For survival analysis, if a subject has not achieved complete cessation of otorrhea by the end of the study, the subject should be considered "censored" at the end of study.

OGD has not previously established a method for equivalence assessment of survival outcome measures. However, the statisticians propose the Kaplan-Meier product limit method (log rank test). The analysis would be facilitated by using the LIFETEST procedure in SAS. There are also some methods for survival data equivalence test available in the literature. For example:

1. Wellek, Stefan. A Log-Rank Test For Equivalence Of Two Survivor Functions (1993), Biometrics 49: 877-881.
2. John Q. Su and L. J. Wei. Nonparametric Estimation For The Difference Or Ratio Of Median Failure Times (1993): Biometrics 49: 603-607.

For the equivalence analysis for time to cessation of otorrhea, the following is proposed:

The compound hypothesis to be tested is:

H_0: $m_T / m_R \leq \theta_1$ or $m_T / m_R \geq \theta_2$

versus

H_A: $\theta_1 < m_T / m_R < \theta_2$

where, m_T = median of test treatment, m_R= median of reference treatment

The standard in OGD for equivalence analyses for continuous endpoints has been θ_1=0.80 and θ_2=1.25.

Two methods could potentially be used to perform the equivalence test. The methods are illustrated for θ_1=0.80 and θ_2=1.25.

3. Perform two one-sided $m_T - 0.8/1.25\ m_R$ tests

H_{01}: $m_T - 0.8\, m_R \leq 0$ versus H_{A1}: $m_T - 0.8\, m_R > 0$

H_{02}: $m_T - 1.25\, m_R \geq 0$ versus H_{A2}: $m_T - 1.25\, m_R < 0$

Multiply all of survival data, time to cessation of otorrhea, from the reference product by 0.8 or 1.25, and then test the resulting data set for equality (α=0.05, one-sided test). This test would be based on the log rank test. Rejection of both null hypotheses H_{01} and H_{02} supports the conclusion of equivalence of the two products.

4. Estimate the 90% CI by using a bootstrap method

The 90% CIs of the median ratio m_T / m_R (corresponding to two 1-sided tests at level α=0.05) could be calculated as follows: 1) obtain medians of test and reference treatment from the Kaplan-Meier product limit method by using the PROC LIFETEST procedure in

SAS®, 2) estimate the ratio m_T / m_R, 3) perform the bootstrap re-sampling approach to obtain the 90% CI for the ratio m_T / m_R.

The null hypothesis H_0 would be rejected if the 90% CI for m_T/m_R is contained in the [0.80, 1.25] interval. Rejection of the null hypothesis H_0 supports the conclusion of equivalence of the two products.

19. The results of the two primary endpoints for both the test product and for the RLD should be compared to the results that supported the approval of the RLD and any historical results in the literature.

20. Study data should be submitted to OGD in electronic format.
    a. A list of file names, with a simple description of the content of each file, should be included.
    b. Provide a .pdf document with a detailed description of the codes that are used for each variable in each of the SAS data sets (for example, Y=yes, N=no for analysis population).
    c. All SAS transport files should include .xpt as the file extension and should not be compressed. A simple SAS program to open the data transport files and SAS files should be included.
    d. Primary data sets should consist of two data sets: No Last Observation Carried Forward (NO-LOCF-pure data set) and Last Observation Carried Forward (LOCF-modified data set).
    e. Provide a separate data set for variables such as demographics, baseline admission criteria, adverse events, reasons for discontinuation of treatment, concomitant medications, medical history, compliance, comments, otorrhea (from subject diary), etc.

21. Provide a summary data set containing a separate line listing for each subject (if data exist) using the following headings, if applicable:
    a. Study identifier
    b. Subject identifier
    c. Site identifier: study center
    d. Age
    e. Age units (years)
    f. Sex
    g. Race
    h. Name of Actual Treatment (exposure): test product, RLD
    i. Duration of Treatment (total exposure in days)
    j. Completed the study (yes/no)
    k. Reason for premature discontinuation of subject
    l. Subject required additional treatment for acute otitis media due to unsatisfactory treatment response (yes/no)
    m. Per Protocol (PP) population inclusion (yes/no)
    n. Reason for exclusion from PP population
    o. Safety population inclusion (yes/no)
    p. Reason for exclusion from safety population
    q. Final designation as clinical cure (yes/no)
    r. Cessation of otorrhea reported (yes/no)
    s. If cessation of otorrhea reported, time to cessation (days)
    t. Treatment compliance: number of missed doses per subject
    u. Concomitant medication (yes/no)
    v. Adverse event(s) reported (yes/no)

Please refer to Table 1 as an example. This sample table may contain additional information not applicable to your study and/or it may not contain all information applicable to your study.

Table 1: Example of a Summary Data Set Containing One Line Listing for Each Subject

STUDYID	SUBJID	SITEID	AGE	AGEU	SEX	RACE	EXTRT	EXDUR	completd	disc_rs	add_trt	pp	pp_rs	safety	safe_rs	clincure	otor_ces	time_ces	complian	CM	AE
101	1	01	10	YEARS	F	1	A	7	Y		N	Y		Y		N	N		0	Y	Y
101	2	01	3	YEARS	F	1	B	7	Y		N	Y		Y		Y	Y	72	0	N	N

Note: Capitalized headings are from Clinical Data Interchange Standards Consortium (CDISC) Study Data Tabulation Model (SDTM) Implementation Guide (IG) for Human Clinical Trials V3.1.2 Final, dated 11/12/08.

STUDYID: Study identifier
SUBJID: Subject identifier for the study
SITEID: Study site identifier
AGE: Age
AGEU: Age units (months, years)
SEX: Sex, M=male, F=female, U=unknown
RACE: Race, e.g., 1=white, 2=Black or African American, 3=Asian, 4=American Indian or Alaska Native, 5=Native Hawaiian or other Pacific Islanders
EXTRT: Name of actual treatment (exposure), e.g., A=test product, B= RLD
EXDUR: Duration of treatment (total exposure in days)
completd: Completed the study, Y=yes, N=no
disc_rs: Reason for premature discontinuation of subject
add_trt: Subject required additional treatment for external otitis media due to unsatisfactory treatment response, Y=yes, N=no
pp: PP population inclusion, Y=yes, N=no
pp_rs: Reason for exclusion from PP population, e.g., A=prematurely discontinued, B=lost to follow-up, C=subject moved out of the area, D=noncompliant, etc.
safety: Safety population inclusion, Y=yes, N=no
safe_rs: Reason for exclusion from Safety population, e.g., A=never treated, etc.
clincure: Final designation as clinical cure, e.g., Y=yes (clinical cure), N=no (failure)
otor_ces: Cessation of otorrhea reported, Y=yes, N=no
time_ces: If cessation of otorrhea reported, time to cessation (days)
complian: Treatment compliance, e.g., number of missed doses per subject
CM: Concomitant medication, Y=yes, N=no
AE: Adverse event(s) reported, Y=yes, N=no

22. Provide a data set containing a separate line listing for each visit per subject (if data exist) using the following headers, if applicable:
    a. Study identifier
    b. Subject identifier
    c. Name of actual treatment (exposure): test product, RLD
    d. Visit number
    e. Visit date

f. Number of days since baseline visit
g. Evaluator: identity of evaluator
h. Cessation of otorrhea reported (yes/no)
i. If cessation of otorrhea reported, time to cessation (days)
j. Concomitant medication reported during this visit (yes/no)
k. Adverse event reported during this visit (yes/no)
l. Laboratory testing during this visit (yes/no)

Please refer to Table 2 as an example. This sample table may contain additional information not applicable to your study and/or it may not contain all information applicable to your study.

Table 2: Example of data set containing one line listing for each visit per subject

STUDYID	SUBJID	EXTRT	VISITNUM	SVSTDTC	ELTMBS	EVAL	otor_ces	time_ces	CMrpt	AErpt	LBtest
101	1	A	1	2004-07-01	0	JB	Y	6	Y	N	Y

Note: Capitalized headings are from Clinical Data Interchange Standards Consortium (CDISC) Study Data Tabulation Model (SDTM) Implementation Guide (IG) for Human Clinical Trials V3.1.2 Final, dated 11/12/08.

STUDYID:	Study identifier
SUBJID:	Subject identifier for the study
EXTRT:	Name of actual treatment (exposure), e.g., A=test product, B=RLD
VISITNUM:	Visit sequence number
SVSTDTC:	Visit date: (SVSTDTC=Subject Visit Start Date Time-Character)
ELTMBL:	Elapsed time since baseline (days)
EVAL:	Evaluator: identity of the evaluator, e.g., initials
otor_ces:	Cessation of otorrhea reported during this visit, Y=yes, N=no
time_ces:	If cessation of otorrhea reported, time to cessation of otorrhea (days)
CMrpt:	Concomitant medication reported during this visit, Y=yes, N=no
AErpt:	Adverse event reported during this visit, Y=yes, N=no
LBtest:	Laboratory testing performed during this visit, Y=yes, N=no

23. These recommendations are specific to this product and may not be appropriate for BE studies of any other product, including any other dosage form or strength of ciprofloxacin hydrochloride and dexamethasone.